

REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 112, are respectfully requested in light of the following remarks.

Upon entry of the foregoing amendments, Claims 1, 2, 4-7, 9-12, 14-16, 18-23, 36, 38-44, 46-49 and 53-60 will be in this application. Claims 3, 8, 24-35, 37, 45 and 50-52 have previously been cancelled without prejudice or disclaimer. Claims 9, 10 and 48 have been withdrawn and are currently amended. Claim 21 has also been withdrawn. Claims 13 and 17 are cancelled in this response, without prejudice or disclaimer. Claims 1, 2, 4, 5, 7, 9 and 10 have been amended to:

- (1) place the definition of R_1 and R_2 , R_3 and R_5 , R_4 , R , T_1 , R_6 , and R_7 in proper Markush group language;
- (2) delete various substituents from the definitions of R_1 and R_2 . The definitions of R_1 and R_2 are amended to also allow R_1 and R_2 to form a heterocycle of 4 to 7 atoms with the nitrogen to which they are attached;
- (3) delete various substituents from the definitions of R_3 and R_5 ;
- (4) delete various substituents from the definitions of R_4 and R_5 , place the definitions in proper Markush group language, replace "hydrocarbon-based" by "hydrocarbon" and replace "possibly" by "optionally";
- (5) delete R_6 , R'_6 , R''_6 and R'''_6 and their definitions;
- (6) delete various substituents from the definition of R ;
- (7) delete R' and its definition;
- (8) delete R_7 , R'_7 , R''_7 and R'''_7 and their definitions;
- (9) delete various substituents from the definition of A ;
- (10) delete various substituents from the definition of T_1 ;

(11) add a new definition of R_6 ; and

(12) add a new definition of R_7 .

Support for R_1 and R_2 forming a heterocycle of 4 to 7 atoms with the nitrogen to which they are attached is found at least on page 10, lines 14-16 of the specification. Support for the new definitions of R_6 and R_7 is found in the deleted definitions of R_6 and R_7 . Support for the new definition of R_6 is also found in the specification on page 11, line 23 – page 12 line 6. Support for the new definition of R_7 is also found in the specification on page 13, lines 1–3. Claim 14 has been amended to depend from Claim 1 rather than from cancelled Claim 13, to replace a heterocycle of 4 to 7 atoms with a furyl group and to define “n” and “m” as being an integer from 1 to 10. Support for these amendments is found in the specification at least on page 26, lines 23-25 and page 19, lines 7-10. Claim 15 has been amended to delete $(CH_2)_nR_8$ from a group represented by R_2 and add the group $(CH_2)_nS-(CH_2)_mR_9$ to represent R_2 . Support for this amendment is found in the specification at least on page 23 line 21 – page 24 line 3 and page 26, lines 5-10. Claim 18 has been amended to depend from Claim 17 rather than from cancelled Claim 17. Claim 48 has been amended to define that the at least one compound of formula (I) or a salt thereof is as defined in Claim 10. Support for this is found in the preamble of Claim 48 itself, which states “The method according to Claim 10.” No new matter has been added in making these amendments. These amendments are made without prejudice or disclaimer and applicants reserve the right to pursue the cancelled subject matter in a continuing application. Applicants are making these amendments to expedite prosecution of the application and to present the Examiner with a reasonable genus for examination encompassing the compounds of Claim 22.

Election/Restriction

The Examiner has said that applicants have traversed the various election of species requirements but has not provided any reasons for traversal. This is incorrect; applicants traversed all requirements for election of species on page 40 of the July 25, 2006 response, third full paragraph.

35 U.S.C. §112 first paragraph Enablement Rejection

Claims 1, 2, 4-7, 11-20, 23, 36, 38-44, 46, 47, 49 and 57-60 have been rejected under 35 U.S.C. §112, first paragraph, as purportedly not reasonably providing sufficient enablement to one of ordinary skill in the art to practice the invention due to the large number of derivatives disclosed in the claims.

Applicants' submit that the amended claims are enabled by the specification. The Examiner has indicated that Claim 22 is enabled. Applicants' submit that the amended claims have been significantly narrowed in the breadth of the compounds claimed and provide a reasonably narrow genus that encompasses the compounds in Claim 22. The amended claims reasonably maintain at least the following chemical properties: molecular size, charge distribution, hydrophobicity, polarity, hydrophilicity and hydrogen bonding. The group of compounds covered by these claims is clearly sufficiently enabled to allow one of ordinary skill in the art to practice the invention as taught in the specification.

The amended claims can no longer be deemed as not enabling because they cover a narrow genus of compounds that closely circumscribes the group of compounds for which the Examiner has indicated there is enablement. Applicants therefore request the withdrawal of the rejections of the claims under 35 U.S.C. §112, first paragraph.

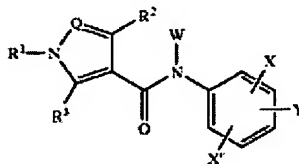
35 U.S.C. §103(a) prior art rejections

Claims 1, 2, 4-7, 11-20, 23, 36, 38-40, 42, 47, 49 and 57 have been rejected under 35 U.S.C. §103(a) as unpatentable over EP 1176140.

Applicants respectfully submit the claims now in the application are not obvious over EP 1176140 and that these claims are allowable.

To establish a *prima facie* case of obviousness, three basic criteria must be met. (MPEP 2143) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

EP 1176140 discloses compounds of the formula:



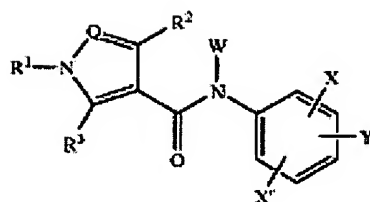
and their medical uses in treating a variety of autoimmune diseases and a variety of other conditions.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation in EP 1176140 to modify the structure of their disclosed compounds to obtain the compounds of the applicants' invention. There is no suggestion or motivation in EP 1176140 to use the compounds for inducing and/or stimulating the growth of keratin fibers and/or

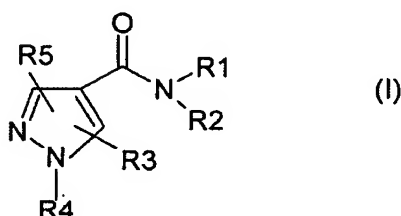
reducing their loss and/or increasing their density. There is no suggestion or motivation in EP 1176140 to use the compounds for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders.

The Examiner has indicated that although EP 1176140 suggests the use of its compounds for treating alopecia, a skilled artisan would not have immediately envisaged the use of the compounds in treating alopecia. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the compounds taught in EP 1176140 for the treatment of hair loss. However as is shown below, the compounds of the applicants' invention are distinct from those taught in EP 1176140 and the analysis below shows that it would not be obvious to one of ordinary skill in the art at the time the invention was made to utilize the compounds of the applicants' invention for the various methods described in the claims. The Examiner further alleges that the instant methodology is considered *prima facie* obvious since EP 1176140 is suggestive of the instant methodology. Applicants respectfully submit that EP 1176140 is not suggestive of the instant methodology for several reasons, including the applicants' use of different compounds, as described below.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There is no reasonable expectation of success based on the teachings in EP 1176140 which disclose the use of different compounds in treating autoimmune diseases and other disorders. The compounds of EP 1176140 have the general structure:

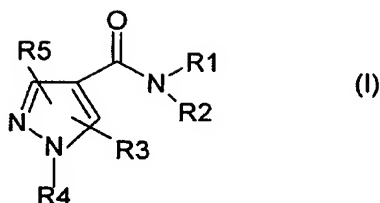


while applicants' compounds have the general structure (I):

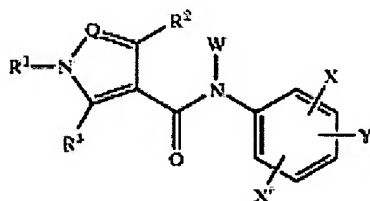


where R_1 and R_2 are not phenyl or a substituted phenyl, but rather are hydrogen or alkyl (optionally substituted by OR_6 or SR_6) or R_1 and R_2 together with the adjacent N from a heterocycle. The differences between the compounds of EP 1176140 and the applicants' compounds are substantial. Applicants' compounds are clearly structurally distinct from those of EP 1176140. With the major structural differences between the prior art compounds and the compounds of the applicants' invention, there would not be a reasonable expectation of success in obtaining the compounds of the applicants' invention, which also have different biological activity than the prior art.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The claims of the applicants' invention are directed towards methods of use of compounds of the general formula:



where R_1 and R_2 are independently selected from the group consisting of hydrogen and saturated or unsaturated, linear or branched C_1 - C_{20} alkyl radicals optionally substituted with at least one substituent T_1 , or R_1 and R_2 form a heterocycle of 4 to 7 atoms with the nitrogen to which they are attached. R_1 and R_2 are not phenyl or a substituted phenyl. However, the compounds of EP 1176140 have a different general structure:



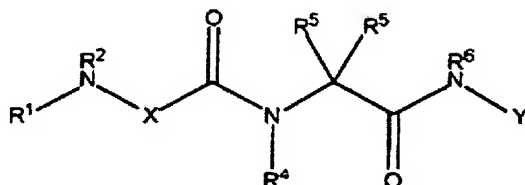
where one of the groups attached to the nitrogen is required to be a phenyl group. EP 1176140 does not teach or suggest the use of the compounds of the applicants' invention. Therefore EP 1176140 does not teach or suggest the compounds of the applicants' invention. Additionally, EP 1176140 does not teach or suggest that the applicants' compounds can be used for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. EP 1176140 does not teach or suggest the use the applicants' compounds for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders. Therefore, EP 1176140 does not teach or suggest all the claim limitations.

Applicants respectfully submit that the claims are not obvious over EP 1176140 and that the rejection should be withdrawn.

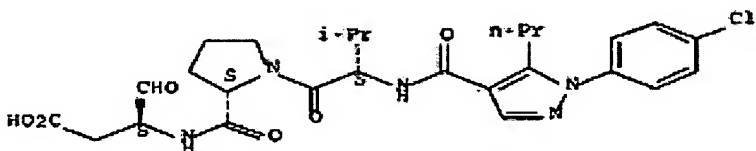
Claims 1, 2, 4-7, 11-20, 23, 36, 38-40, 42, 47, 49 and 57 have been rejected under 35 U.S.C. §103(a) as unpatentable over WO 99/47545.

Applicants respectfully submit the claims herein are not obvious over WO 99/47545 and that these claims are allowable.

WO 99/47545 discloses use of compounds of the structure:



as inhibitors of capsases. The Examiner has cited the compound below among the compounds disclosed in WO 99/47545:



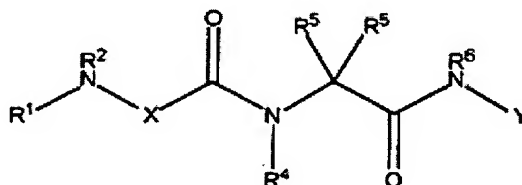
WO 99/47545 teaches the use of these compounds in treating a wide variety of diseases and disorders, including alopecia.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation WO 99/47545 to modify the structure of their disclosed compounds to obtain the compounds of the applicants' invention. There is no suggestion or motivation in WO 99/47545 to use

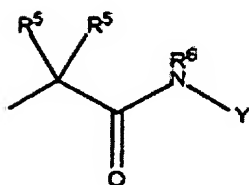
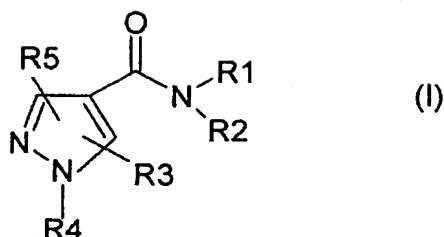
the compounds of the applicants' invention for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. There is no suggestion or motivation in WO 99/47545 to use the compounds of the present invention for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There is no reasonable expectation of success based on the teachings in WO 99/47545, which disclose the use of different compounds in inhibiting capsases, to obtain methods for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density using compounds with a different structure. There is no reasonable expectation of success based on the teachings in WO 99/47545 to obtain methods for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders using compounds with a different structure than taught in WO 99/47545.

The compounds of WO 99/47545 have the general structure:



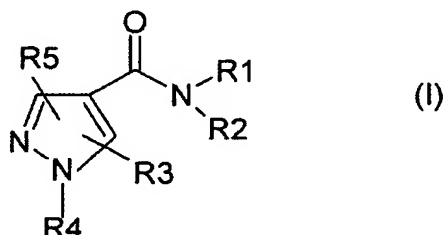
while applicants' compounds have the general structure (I):



where R₁ and R₂ are not

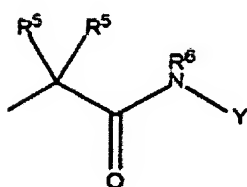
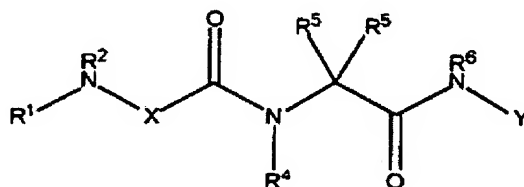
The differences between the compounds of EP 1176140 and the applicants' compounds are substantial. With the major structural difference between the prior art compounds and the compounds of the applicants' invention, there would not be a reasonable expectation of success in obtaining the compounds of the applicants' invention, which have different biological activity than the prior art.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The claims of the applicants' invention are directed towards methods of use of compounds of the general formula:



where R₁ and R₂ are independently selected from the group consisting of hydrogen and saturated or unsaturated, linear or branched C₁-C₂₀ alkyl radicals optionally substituted with at least one substituent T₁, or R₁ and R₂ form a heterocycle of 4 to 7

atoms with the nitrogen to which they are attached. However, the compounds of WO 99/47545 have a different general structure:



The portion of the molecule attached to nitrogen is not present in the compounds used in the methods of the applicants' invention. WO 99/47545 does not teach or suggest the use of the compounds of the applicants' invention. Therefore WO 99/47545 does not teach or suggest the compounds of the applicants' invention. Additionally, WO 99/47545 does not teach or suggest that the applicants' compounds can be used for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. WO 99/47545 does not teach or suggest the use the applicants' compounds for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders. Therefore, WO 99/47545 does not teach or suggest all the claim limitations.

Applicants respectfully submit that the claims are not obvious over WO 99/47545 and that the rejection should be withdrawn.

Claims 43, 44, 46, 59 and 60 have been rejected under 35 U.S.C. §103(a) as unpatentable over EP 1176140 or WO 99/47545 in view of Bradbury et al. (US 6,124,362).

Applicants respectfully submit these claims are not obvious over EP 1176140 or WO 99/47545 in view of Bradbury et al. and these claims are allowable.

Bradbury et al. discloses a method for regulating the growth and loss of hair using compositions comprising a compound selected from the group consisting of lupine triterpenes, derivatives of oleanane triterpenes, derivatives of ursane triterpenes and salts and mixtures thereof. As previously shown above, there is a basic deficiency in the primary references in that the applicants' claims are not obvious over EP 1176140 or WO 99/47545 for a variety of reasons. The combination of Bradbury et al. with these references does not cure this basic deficiency.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation in EP 1176140, WO 99/47545 or Bradbury et al. to use the compounds of the applicants' invention for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. There is no suggestion or motivation in and of these references to use the compounds of the applicants' invention for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There is no reasonable expectation of success based on

the teachings in EP 1176140, WO 99/47545 and Bradbury et al. to obtain methods for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density using compounds with structures significantly different from that taught in the prior art. There is no reasonable expectation of success based on the teachings in EP 1176140, WO 99/47545 and Bradbury et al. to obtain methods for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders using compounds with different structures than taught in the prior art. There would not be a reasonable expectation of success in arriving at the applicants' invention using the teachings of the cited prior art.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. EP 1176140, WO 99/47545 and Bradbury et al. do not teach or suggest the use of the compounds of the applicants' invention. EP 1176140, WO 99/47545 and Bradbury et al. do not teach or suggest using the compounds of the applicants' invention for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. EP 1176140, WO 99/47545 and Bradbury et al. do not teach or suggest using the compounds of the applicants' invention for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders. Therefore, the prior art references, either alone or combined, do not teach or suggest all the claim limitations.

Applicants respectfully submit that none of the claims is obvious over EP 1176140, WO 99/47545 and Bradbury et al. and that the rejection should be withdrawn.

Claims 43, 44, 46, 59 and 60 have been rejected under 35 U.S.C. §103(a) as unpatentable over EP 1176140 or WO 99/47545 in view of Rosenbaum et al. (US 5,443,823).

Applicants respectfully submit that these claims are not obvious over EP 1176140 or WO 99/47545 in view of Rosenbaum et al. and that these claims are allowable.

Rosenbaum et al. disclose a method for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss using compositions comprising two components, a pyrimidine derivative of a specific formula and a salicylic acid derivative. Rosenbaum et al. disclose that the combination of a salicylic acid derivative with said pyrimidine derivative greatly modifies the solubility of the pyrimidine derivative and allows a faster dissolution of the pyrimidine derivative. As previously shown in this paper, there is a basic deficiency in the primary references in that the applicants' claims are not taught or suggested by EP 1176140 or WO 99/47545 for a variety of reasons. The combination of Rosenbaum et al. with these references does not cure this basic deficiency.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation in EP 1176140, WO 99/47545 or Rosenbaum et al. to use the compounds of the applicants' invention for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. There is no suggestion or motivation in and of these references to use the compounds of the applicants' invention for inhibiting

15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There is no reasonable expectation of success based on the teachings in EP 1176140, WO 99/47545 and Rosenbaum et al. to obtain methods for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density using compounds with structures different from that taught in the prior art. There is no reasonable expectation of success based on the teachings in EP 1176140, WO 99/47545 and Rosenbaum et al. to obtain methods for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders using compounds with different structures than taught in the prior art. Therefore, there would not be a reasonable expectation of success in arriving at the applicants' invention using the teachings of the cited prior art.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. EP 1176140, WO 99/47545 and Rosenbaum et al. do not teach or suggest the use of the compounds of the applicants' invention. EP 1176140, WO 99/47545 and Rosenbaum et al. do not teach or suggest using the compounds of the applicants' invention for inducing and/or stimulating the growth of keratin fibers and/or reducing their loss and/or increasing their density. EP 1176140, WO 99/47545 and Rosenbaum et al. do not teach or suggest using the compounds of the applicants' invention for inhibiting 15-hydroxyprostaglandin dihydrogenase and treating 15-hydroxyprostaglandin dihydrogenase disorders. Therefore, the prior art

references, either alone or combined, do not teach or suggest all the claim limitations.

Applicants respectfully submit that none of the claims is obvious over EP 1176140, WO 99/47545 and Rosenbaum et al. and that the rejection should be withdrawn.

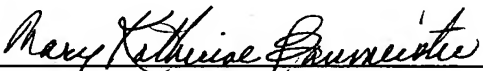
In view of the foregoing, it is believed that the record rejections cannot be maintained against the amended claims. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

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